

REMARKS

Claims 134, 139-143, 145 and 148-175 are active in this application. Favorable reconsideration is respectfully requested.

The rejection of the claims under 35 U.S.C. §112, second paragraph, is believed to be obviated by the amendments submitted above. Claim 134 has been amended such that there is antecedent basis. Claims 143 and 166 have been amended to delete the phrase “which anchors said C-terminal fragment to a membrane of a eukaryotic cell expressing a MSP-1 protein.”

In view of the foregoing, the claims are definite within the meaning of 35 U.S.C. §112, second paragraph. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Longacre in view of Longacre et al. is respectfully traversed. These references fail to suggest the claimed composition.

Longacre describes the C-terminal sequence of *Plasmodium cynomolgi* merozoite surface protein 1 and its homologies with other *Plasmodium* species. This reference fails to disclose or even suggest a MSP-1 protein with the atomic coordinates and fingerprints as recited in the claims. In addition, this reference fails to disclose or suggest using alum as an adjuvant in a vaccinating composition.

Longacre et al. disclose *Plasmodium vivax* merozoite surface protein 1 recombinant proteins, which were produced in baculovirus. *Plasmodium vivax* is excluded from independent Claim 134. Moreover, Longacre et al. fail to disclose that alum can be used in the vaccinating composition.

The present specification clearly discloses that this was the first time significant protection could be achieved using a recombinant MSP-1 protein and alum, which is evidenced at page 27 of the specification, which states the following:

While the results are a little less spectacular than the preceding results (Figures 6, 8), this is the first time that significant protection has been observed from recombinant MSP-1 with alum.

Some of the results obtained in the specification were obtained by using complete and incomplete Freund's adjuvant, which cannot be administered to man.

Therefore, it was an unexpected result that the adjuvant alum would in fact work with the recombinant MSP-1 19 kilodalton C-terminal fragment, since it was known in the art at the time of filing of the present application that adjuvants played a critical role in determining the specificity of the immune response to the antigens of *Plasmodium* species. There was no expectation of success that the alum would in fact be an adjuvant that would in fact work with the recombinant C-terminal MSP-1 19 kilodalton fragments.

Absent any demonstration that alum and a recombinant C-terminal MSP-1 19 kilodalton fragment can achieve an immune response in these prior art references, this rejection cannot be maintained. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Longacre in view of Longacre et al. and further in view of Holder et al. is respectfully traversed. These references fail to suggest the claimed composition.

As discussed above, neither Longacre nor Longacre et al. disclose that alum can be used successfully as an adjuvant in combination with recombinant C-terminal MSP-1 19 C-terminal fragment from a *Plasmodium* parasite.

Holder et al. disclose EGT-like domains from the MSP-1 protein. Although this reference mentions that these sequences can be used as vaccines and can be administered with an appropriate adjuvant such as alum, all of the examples illustrating some protective immune response of the EGT-like proteins used Freund's complete or incomplete adjuvant.

It was not predictable whether the adjuvant of alum in combination with recombinant C-terminal MSP-1 19 C-terminal fragment from *Plasmodium* parasite could achieve any immune response. Holder et al. fail to demonstrate that alum could be achieved any immune response. Holder et al. fail to demonstrate that alum could be used as an adjuvant in combination with EGF-like domains and an immune response was achieved.

In view of the fact that Holder et al. does not show any immune response using the EGF-like domains with alum, Applicants submit that a skilled artisan would not have any expectation of success that a 19 kilodalton C-terminal fragment of an MSP-1 protein of a *Plasmodium* parasite and alum can be effective in a vaccinating composition. This is because there was at the time of filing of the present application an unpredictability in the malaria art of whether an immune response could be achieved using certain adjuvants, other than Freund's adjuvant, in conjunction with recombinant malaria constructs.

Thus, without such expectation of success the presently claimed invention should not be rendered obvious, since there must be a reasonable expectation of success coupled with a suggestion in the art in order for an invention to be deemed obvious. See In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moreover, Holder et al. fail to disclose that alum when used in conjunction with a C-terminal MSP-1 protein, more specifically EGF-1 or EGF-2, has a better immune response than Freund's, as demonstrated in the present invention. See Figure 10A and 10B of the specification which show that less parasitemia was observed in squirrel monkeys immunized with MSP-1 p19 and alum than with MSP-1 p19 and Freund's. This unexpected result is neither demonstrated nor suggested in Holder et al.

Since Holder et al. is silent with respect to a diminution of parasitemia when alum is used as an adjuvant in comparison with Freund's, Applicants submit that the combination of references fails to render obvious the presently claimed invention to the skilled artisan. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Chappel et al., Miller et al., Longacre et al. and Longacre is respectfully traversed. These references fail to suggest the claimed composition.

It will be demonstrated below that none of these references alone or in combination teach or suggest modifying the specific constructs to achieve those of Claims 151 and 152 and those claims dependent thereon. Furthermore, there is absolutely no teaching or even suggestion of the oligomer claims of Claims 167, 168, 170, 171 or 173.

Chappel et al. disclose monoclonal antibodies that inhibit *Plasmodium falciparum* invasion *in vitro* and recognize the first growth-factors-like domain of the merozoite surface protein 1.

It appears that the Examiner focuses on the three recombinant constructs described in Chappel et al. Two of these constructs contain the MSP1EGF1 and MSP1EGF2 regions fused to glutathione S-transferase. These two recombinant proteins are fusion proteins, which have nothing in common with the claims set forth in the present rejection. Also the sequences from MSP1 are shorter sequences containing a nucleic acid sequence encoding 47 and 52 amino acids respectively from MSP1EGF1 and MSP1EGF2.

The third recombinant construct is an insect cell product, S42 $\Delta$ A contains a nucleic acid sequence encoding 271 amino acids from the Wellcome strain of MSP1, including both EGF-like domains fused to nucleic acid sequence encoding 34 amino acids of MSP1 to provide a signal for secretion.

None of these constructs recites a recombinant protein comprising a leader sequence from *Plasmodium vivax* having a nucleic acid sequence encoding 32 amino acids and a 19 kilodalton C-terminal MSP-1 fragment from *Plasmodium falciparum* containing a nucleic acid sequence encoding 92 amino acid sequences (Claim 151) or 113 amino acid sequences (Claim 153) as claimed.

Moreover, there is no suggestion to those skilled in the art to modify any of these constructs. Furthermore, Chappel et al. do not demonstrate or clearly suggest that these constructs set forth therein can inhibit parasitemia *in vivo* with a host infected with a *Plasmodium* parasite, as recited in the claims and is silent with respect to the claimed oligomers.

Miller et al. was cited to confirm the numbering of the S42 $\Delta$ A construct described in Chappel et al. The fact that the Examiner has cited this reference and has focused on the specific S42 $\Delta$ A construct is a clear indication that the Examiner is using hindsight in this rejection. Of course, hindsight is not acceptable in making a rejection under 35 U.S.C. §103(a).

Longacre et al. disclose *Plasmodium vivax* MSP-1 C-terminal recombinant proteins produced in baculovirus. These recombinant constructs have a leader sequence of 35 bp and contain a nucleic acid sequence encoding 401 amino acids or 124 amino acids (anchored form) and 379 amino acids or 102 amino acids (secreted form). Moreover, Longacre et al. fail to demonstrate that their constructs can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite, as recited in the claims. Moreover, there is no disclosure of oligomers as set forth in Claims 167, 168, 170, 171 and 173.

Longacre described *Plasmodium cynomolgi* MSP-1 C-terminal sequence and its homologies with other *Plasmodium* species. There is no demonstration in this reference that any of these disclosed sequences can achieve inhibition of parasitemia *in vivo* in a host infected with a *Plasmodium* parasite. There is also no disclosure of oligomers, as presently claimed.

In the Official Action dated August 24, 2004, the Examiner states that it would have been well within the skilled artisan to substitute the *P. vivax* signal and anchoring sequences of the homologous sequences of *P. falciparum* and as such the immunological function of *P. falciparum* would not have been influenced. However, as taught in Longacre et al., there is no cross-reactive immunity between *P. vivax* baculovirus recombinants and those of *P. falciparum*. This is evidenced at least on page 203 of Longacre et al., which states:

Since the baculovirus recombinants from this region appear to retain many conformational epitopes of the native protein, the question of cross reactivity between *P. vivax* and *P. falciparum* MSP1 molecules could be addressed. We were unable to demonstrate any cross reactivity of our baculovirus recombinant protein by immunoblot under non reducing conditions with either polyclonal rabbit antisera against affinity purified *P. falciparum* MSP1 [45] or monoclonal antibodies 1114.4 and 111.5 directed against C-terminal conformation epitopes [7].

Therefore, one skilled in the art would not definitely consider substituting *P. vivax* with *P. falciparum* and expect to achieve the same immunological function.

Finally, the combination of these references fails to render the presently claimed invention obvious since none of these references demonstrate that the recombinant constructs can achieve inhibition of parasitemia in vivo in a host inflicted with a *Plasmodium* parasite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Chappel et al., Miller et al., Longacre et al., Longacre, and further in view of Holder et al. is respectfully traversed. These references fail to suggest the claimed composition.

Chappel et al., Miller et al., Longacre and Longacre et al. are discussed above. Applicants submit that the conclusion that can be reached in the combination of these references is that one skilled in the art would not be persuaded to substitute similar recombinant constructions for *P. vivax* with *P. falciparum* and expect to maintain the same immunological function. This is especially in view of the fact that the monoclonal antibodies 111.2 and 111.4 described in Chappel et al. did not cross react with the baculovirus produced *P. vivax* constructs described in Longacre et al.

As discussed above, Holder et al. fail to disclose that alum when used in conjunction with a C-terminal MSP-1 protein, more specifically EGF-1 or EGF-2, has a better immune response than with Freund's. This is demonstrated in Figure 10A and 10B in the specification wherein less parasitemia was observed in squirrel monkeys immunized with MSP-1 p19 and alum than with MSP-1 p19 and Freund's. This unexpected result is neither demonstrated nor contemplated in Holder et al.

Thus, Applicants submit that the combination of these references lack the necessary criteria to render the presently claimed invention obvious. Withdrawal of this ground of rejection is respectfully requested.

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Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

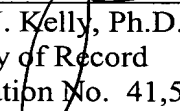
Respectfully submitted,

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